

Bloodstream Infection, Venous Thrombosis, and Peripherally Inserted Central Catheters: Reappraising the Evidence

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ABSTRACT:

The widespread use of peripherally inserted central catheters (PICCs) has transformed the care of medical and surgical patients. Whereas intravenous antibiotics, parenteral nutrition, and administration of chemotherapy once necessitated prolonged hospitalization, PICCs have eliminated the need for such practice. However, PICCs may not be as innocuous as once thought; a growing body of evidence suggests that these devices also have important risks. This review discusses the origin of PICCs and highlights reasons behind their rapid adoption in medical practice. We evaluate the evidence behind 2 important PICC-related complications—venous thrombosis and bloodstream infections—and describe how initial studies may have led to a false sense of security with respect to these outcomes. In this context, we introduce a conceptual model to understand the risk of PICC-related complications and guide the use of these devices. Through this model, we outline recommendations that clinicians may use to prevent PICC-related adverse events. We conclude by highlighting important knowledge gaps and identifying avenues for future research in this area.

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KEYWORDS: Central line-associated bloodstream infections; Peripherally inserted central catheters; Venous thrombosis

Whereas intravenous antibiotics, parenteral nutrition, and administration of chemotherapy once required prolonged hospitalizations, the growing availability of peripherally inserted central catheters (PICCs) has virtually eliminated the need for this practice.¹⁻⁴ This review provides a historical overview of PICCs and describes factors promoting PICC use. We summarize the literature regarding complications associated with PICCs and introduce a domain-based, conceptual framework through which clinicians may better understand these risks. By using this model, we present evidence-based strategies to prevent adverse outcomes.

MATERIALS AND METHODS

We performed a literature search of multiple databases, including MEDLINE via Ovid (1946 to the present), EMBASE (1946 to the present), BIOSIS (1926 to the present), EBM Reviews via Ovid including Cochrane CENTRAL (1960 to the present), and Conference Papers Index via ProQuest (1982 to the present) for key terms, including *peripherally inserted central catheter*, *PICC*, *venous thrombosis*, *bloodstream infection*, and *central line-associated bloodstream infection*. All human studies published in full text, abstract, or poster form were included. A total of 475 articles were retrieved by this search (last updated February 13, 2012). For this narrative review, we concentrated on studies that reported on the complications of bloodstream infection and venous thromboembolism associated with PICCs in adults.

Historical Origins of the Peripherally Inserted Central Catheter

Although the concept of a long-term venous access device had been considered previously,⁵ the successful use of a

Funding: None.

Conflict of Interest: None.

Authorship: All authors had access to the data and played a role in writing this manuscript.

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peripherally inserted, centrally located catheter was first reported in 1975.⁶ In a case series, Hoshal⁶ placed a 61-cm silicone catheter into the superior vena cava through the basilic or cephalic veins for total parenteral nutrition. Although 6 catheters were discontinued prematurely for “venous and nonvenous reactions,” 30 lasted the entire duration of parenteral necessity (range 4-56 days).

Although technologic progress has led to novel polyurethane compounds and an array of configurations, little of Hoshal’s original approach to PICC placement has changed. However, the clinical indications for PICCs have expanded to include tasks as diverse as long-term antibiotic delivery, parenteral nutrition, delivery of irritant/vesicant medications (eg, chemotherapy), establishment of vascular access in patients with difficult venous anatomies, and even central venous pressure monitoring.⁷

Factors Promoting Widespread Peripherally Inserted Central Catheter Use

Although today’s physician is presented with a selection of venous catheter choices with inherent advantages and disadvantages (Table 1), PICC use has specifically grown in hospitals across the United States.^{1,8,9} Several factors may explain this development. First, owing to its peripheral site of entry, PICC insertion is easier and safer than that of conventional venous catheters.¹⁰ Second, PICCs eliminate the pain associated with phlebotomies or routine replacement of peripheral intravenous catheters. In one of the few randomized controlled trials involving these devices, PICCs effectively reduced needle punctures, improved patient satisfaction, and were cost-effective in a cohort of surgical patients.¹¹ In an era of patient satisfaction, it is not inconceivable that providers may preferentially turn to a device that minimizes patient discomfort. Third, a unique prevailing practice paradigm involves the use of “vascular access teams” to insert PICCs. These teams are typically composed of registered nurses who (with specific training) occupy niche roles dedicated to venous access.^{10,12} The development of these teams may have created the perfect prescribing privilege for physicians, who have been demonstrated to rely on nursing-led PICC placement when peripheral intravenous access is not routinely available.¹³ Finally, PICCs are perceived as being safer than central venous catheters. Because the initial evidence supported this viewpoint, this perspective likely played a salient role in expanding PICC use.¹⁴⁻¹⁸

CLINICAL SIGNIFICANCE

- The use of PICCs has grown in hospitalized, critically ill, and ambulatory patients.
- Despite widespread use, scant data regarding the prevalence, patterns and appropriateness of PICC use exists.
- PICCs are associated with venous thromboembolism and bloodstream infections, complications that may offset any perceived benefit(s) from these devices.
- A research agenda examining patterns of use, complications, and comparative risks and benefits of PICCs in well-defined populations is needed.

Evidence Regarding Peripherally Inserted Central Catheter–Related Complications

Despite the widespread adoption of PICCs, accumulating evidence suggests that they are associated with important complications, including bloodstream infection and venous thrombosis (Table 2).¹⁹⁻²¹ The literature regarding these adverse events emanates from 2 distinct patient populations: those with and without cancer. Because important differences exist between these patients with respect to PICC-related bloodstream infections and thrombosis, these subsets are examined separately.

Adult Patients Without Malignancies

Central Line-Associated Bloodstream Infection. A central line-associated bloodstream infection occurs when a patient with an indwelling central venous catheter develops bacteremia in the absence of another identifiable source. Central line-associated bloodstream infections are significant because they

prolong hospitalization, increase mortality, and increase healthcare costs.^{22,23} Many clinicians believe that PICCs are associated with a lower-risk of central line-associated bloodstream infection than other venous catheters. Various quasi-scientific explanations were proffered to support this viewpoint, including the fact that lower temperatures and lesser bacterial colonization over the skin of the upper arm (vs that of the neck, groin, or chest) decreased the risk of bacterial entry into the bloodstream during line insertion.^{24,25} Initial studies supported this hypothesis, finding PICC-related bloodstream infection rates of 0.4 to 0.8 per 1000 catheter days, an incidence significantly lower than the 2.0 to 5.0 central line-associated bloodstream infections per 1000 catheter days reported for other catheter types.^{8,14-16,18}

However, a number of investigators have challenged this belief. In a prospective cohort study, Safdar and Maki²⁶ found that PICCs placed in hospitalized patients were associated with 2.1 bloodstream infections per 1000 catheter days. In an accompanying systematic review of the literature, subgroup analysis showed that inpatient PICC insertion was associated with twice the rate of bloodstream infection than outpatient placement (2.1 [95% confidence interval {CI}, 1.0-3.2] vs 1.0 [95% CI, 0.8-1.2] per 1000 catheter days). The authors theorized that inadvertent selection of healthier patients in ambulatory settings might have confounded the low-rate of PICC-related bloodstream infections in the literature.²⁶ Supportively, Shuman et al²⁷ found that PICCs were the most common device associated

Table 1 General Types, Advantages, and Disadvantages of Venous Catheters

	Description	Advantages/Disadvantages
Nontunneled catheters	Short (12-15 cm) venous catheters inserted into the internal jugular, subclavian, or femoral veins. Typically feature 1-3 lumens for access.	Ideal for short-term or emergency venous access. Femoral site less favored owing to increased risk of bloodstream infection. Insertion can be done at bedside.
Midline catheters	Mid-length (10-20 cm) venous catheters inserted into the veins of the upper extremity (cephalic, basilic, brachial) that have been modified such that their tip resides in a large, noncentral vein. Typically used when full-length PICCs are relatively contraindicated (eg, in patients with end-stage renal disease).	Decreased risk of phlebitis and venous occlusion compared with triple-lumen catheters or PICCs. Does not require radiographic confirmation of tip location. Insertion risk includes local or deep injury. Limited in durability and duration of access. Associated with similar risk of CLABSI as PICCs. Recommended if venous access > 6 d is anticipated.
Peripherally-inserted central catheters	Long (30-40 cm) venous catheters inserted into the veins of the upper extremity (cephalic, basilic, brachial). Typically terminate in the superior vena cava/cavoatrial junction.	Can be inserted by nursing-led PICC teams. Insertion risks include local or deep injury. Risk of thrombosis and infection may outweigh benefits in particular patient populations.
Tunneled catheters	A larger-bore catheter that is tunneled under the skin such that it terminates in a central vein of choice. Available in cuffed and noncuffed varieties.	Tunneled path helps prevent infection because site of entry on skin remains distal to that of vein entry. Insertion is usually complex and requires fluoroscopic monitoring and anesthesia. Risk of complications includes hematoma, local injury, and deep injury. Insertion success is highly operator dependent.

CLABSI = central line-associated bloodstream infection; PICC = peripherally inserted central catheter.

with central line-associated bloodstream infection among critically ill patients in 2 intensive care units. In another study, Ajenjo et al¹³ observed that rates of PICC bloodstream infection were higher in those admitted to an intensive care unit compared with non-intensive care unit areas (4.79 vs 2.79 episodes per 1000 catheter-days; relative risk, 1.7; 95% CI, 1.10-2.61).¹³ In a prospective study restricted to hospitalized patients, Al Raiy et al²⁸ found virtually identical central line-associated bloodstream infection rates in patients with PICCs compared with central venous catheters, suggesting that PICCs are not necessarily “safer” than conventional venous catheters.

Peripherally Inserted Central Catheter-Related Venous Thromboembolism. Several studies have drawn attention to the risk of thrombosis related to PICC placement in adults without cancer.^{1,20,29-32} In a retrospective cohort analysis of PICC-related venous thromboembolism at the Cleveland Clinic, 51 of 2063 patients (2.47%) experienced PICC thrombosis.³² In the only randomized controlled trial comparing PICC use with peripheral intravenous lines in adults, PICCs were associated with a substantial risk of deep vein thrombosis (relative risk, 6.6; $P = .03$).²⁰ In a single-center study of hospitalized patients, the incidence of PICC thrombosis was 4.89% and those with prior venous thromboem-

bolism were at extraordinary risk for this outcome (odds ratio [OR], 10.83; 95% CI, 4.89-23.95).³³ In a multivariate model examining predictors of thrombosis, Evans et al³⁴ found that increasing PICC diameter, surgery lasting 1 hour or more, and a history of deep vein thrombosis were independently associated with PICC-related venous thromboembolism. A study in a cohort of neurosurgical intensive care patients with PICCs also found that those undergoing surgery for 1 hour or more (OR, 3.26; 95% CI, 1.48-7.17) and those with prior venous thromboembolism (OR, 6.66; 95% CI, 2.38-18.62) were at greater risk for PICC-related venous thromboembolism. Of note, the study also reported that PICC placement in a paretic arm (OR, 9.85; 95% CI, 4.42-21.95) and infusion of mannitol (OR, 3.27; 95% CI, 1.27-8.43) increased venous thromboembolism risk.³⁵ Finally, a recent study seeking to simplify the prediction of venous thromboembolism in hospitalized patients found that prior thromboembolism, an order for bed rest, cancer diagnosis, and presence of a PICC were most predictive of venous thromboembolism at 90 days.³⁶

Adult Patients with Malignancies

Because reliable vascular access is a prerequisite for chemotherapy administration, blood sampling, transfusions, antimicrobial therapy, and nutrition in patients with malig-

Table 2 Immediate and Delayed Complications Associated with Peripherally Inserted Central Catheters**Immediate Complications**

Injury to nerve, muscle, and deep tissue at site of insertion
 Phlebitis at site of insertion
 Air embolism during insertion
 Hematoma at insertion site
 Atrial or ventricular arrhythmias (guidewire related)
 Catheter migration/breakage/coiling or malpositioning

Delayed Complications

PICC-related bloodstream infection
 PICC-related venous thrombosis and pulmonary embolism
 Catheter migration/breakage/coiling or malfunction

PICC = peripherally inserted central catheter.

nancy, the use of PICCs in cancer is increasing.^{26,34,37} The presence of immunosuppression related to disease and therapy, thrombocytopenia, and coagulopathy substantially influences the risk of catheter-related infectious and thrombotic complications in this patient population (**Table 3**).

Central Line-Associated Bloodstream Infection. The precise incidence of PICC-related bloodstream infections in patients with cancer remains uncertain owing to conflicting study results.^{31,38-42} For instance, in a cohort of patients with hematologic malignancies, Worth et al³⁷ found no significant difference in bloodstream infections between PICCs and nontunneled central venous lines. However, in a prospective study of adult patients with both hematologic and solid tumor malignancies, Mollee et al³⁹ observed that PICCs were associated with a lower risk of central line-associated bloodstream infection than tunneled and nontunneled central lines. These divergent findings may relate to variations in the definition of central line-associated bloodstream infection. For example, a recent systematic review found no citation or definition for bloodstream infection in 39 of 191 studies of central line-associated bloodstream infection in patients with cancer!⁴³

These issues notwithstanding, the evidence almost uniformly reports higher rates of PICC-related bloodstream infections in adult patients with cancer than in those without malignancies (1.1 vs 1.8 to 7.7 per 1000 PICC days).^{8,37,41} Moreover, the development of central line-associated bloodstream infection in patients with malignancy may herald ominous consequences. In one study, crude mortality rates of nosocomial central line-associated bloodstream infection were as high as 36% for neutropenic and 31% for non-neutropenic patients with malignancies.⁴⁴

Peripherally Inserted Central Catheter-Related Thrombosis and Venous Thromboembolism. The precise incidence of PICC-related thrombosis in patients with malignancy is unknown. A systematic review encompassing 63 studies of venous catheter-related thrombosis in patients with cancer reported an incidence rate from 0.3% to

28.3%.⁴⁵ In a prospective trial of patients with various cancers who primarily underwent PICC placement (65%), a symptomatic thrombosis rate of 4.3% was reported.⁴⁶ Recent data derived from large, prospective trials of thromboprophylaxis suggest a symptomatic thrombosis incidence of 4% to 8% in patients with cancer, although these data are limited by the fact that other central venous catheters also were included.⁴⁷ Multiple single-center studies have reported PICC-related venous thromboembolism rates between 3.4% and 7.8%.^{40-42,48,49,50} As expected, venous thromboembolism estimates in patients with cancer consistently exceed those of patients without cancer. A recent meta-analysis of venous thromboembolism restricted to those with malignancy not only confirmed this finding but also identified PICCs as being associated with a significantly increased thrombosis risk compared with tunneled catheters.⁵¹ The most recent study examining this question reaffirmed this conclusion, finding that only enlarging PICC diameter and malignancy were associated with PICC-related deep vein thrombosis.⁵²

Although cancer inherently increases the risk for thrombosis, several factors related to PICCs themselves may increase the likelihood of venous thromboembolism. For example, a retrospective analysis of patients with hematologic malignancy found that when practice was changed to insert PICCs through a tunneled fashion in the internal jugular vein, the PICC-related thrombosis rate declined from 7.8% to 0.4%.⁵³ This dramatic decline suggests that route of access may influence thrombosis risk. Likewise, subclavian vein insertion and improper catheter tip location were independent risk factors for PICC-related thrombosis in 2 separate studies.^{49,51} Although a direct association between tunneled catheter size and venous thromboembolism has been reported in patients with malignancy, whether a similar relationship holds true for PICCs in patients with cancer is unknown.⁵⁴

Strategies to Prevent Peripherally Inserted Central Catheter-Related Complications

A thoughtful evaluation of the risk of bloodstream infection and thrombosis weighed against the benefit of PICC placement represents the first step in preventing PICC-related central line-associated bloodstream infection and venous thromboembolism. In the absence of large, randomized prospective studies to guide this decision, we offer a pragmatic approach for clinicians through a conceptual framework rooted in the domains of patient-, provider-, and device-related risk factors (**Figure**). Although this model lacks external validation, it is evidence-based, convenient, and applicable to both patients with and without cancer.

Prevention of Peripherally Inserted Central Catheter-Related Bloodstream Infection. Clinicians may focus on preventing PICC-related bloodstream infections by identifying patient-, catheter-, and provider-specific risk factors associated with this outcome. In both patients with and without malignancy, established patient-specific risks for

Table 3 Important Differences in Peripherally Inserted Central Catheter-Related Bloodstream Infection and Venous Thromboembolism Between Patients with and without Cancer^{9,21,27,30,32-35,38,39,42,44,46,47,51,54,56,58,60,64,65,67}

	Patients without Cancer	Patients with Cancer
Bloodstream Infection		
Incidence and mortality	Incidence: 1.0 to 2.1 per 1000 catheter days Estimated mortality risk: 12%-25%	Incidence: 1.81 to 7.71 per 1000 catheter days Estimated mortality risk: 31%-36%
Patient risk factors	Severe or critical illness No. of prior central venous catheter insertions	Severe or critical illness Underlying cancer diagnosis (greatest for aggressive hematologic malignancy, least for esophageal and colorectal cancers) No. of prior central venous catheter insertions
Device risk factors	No. of PICC lumens Duration of catheter placement	No. of PICC lumens Duration of catheter placement Right-sided line insertions (greater risk of CLABSI)
Provider risk factors	Early removal of catheter Approach via internal jugular route (lowered risk of CLABSI) Adherence to universal, aseptic precautions when accessing and maintaining PICC lines Monitoring for signs of erythema, warmth at site of device entry	Early removal of catheter Approach via internal jugular route (lowered risk of CLABSI) Adherence to universal, aseptic precautions when accessing and maintaining PICC lines Monitoring for signs of erythema and warmth at site of device entry Avoidance of PICC lines in neutropenic/high-risk patients
Catheter-Related Thrombosis		
Incidence and mortality	Incidence: varies from 2.0%-5.5% Estimated mortality risk: 1%-2%	Incidence: varies from 3.4% to 7.8% Estimated mortality risk: 2%-4%
Patient risk factors	Operative procedure lasting > 1 h History of VTE	History of VTE Prior venous catheter insertion Underlying hematologic malignancy (greater risk of VTE)
Device risk factors	Catheter tip in site other than cavoatrial junction PICC diameter/gauge	Catheter tip in site other than cavoatrial junction Approach via subclavian venipuncture route (greater risk of VTE)
Provider risk factors	Vigilance for VTE often low Use of prophylactic anticoagulation Infusion of specific drugs (eg, mannitol, vancomycin) increases risk for VTE Insertion into a paretic limb (greater risk of VTE)	Vigilance for VTE greater (early diagnosis and treatment) Use of prophylactic anticoagulation Multiple insertion attempts

PICC = peripherally inserted central catheter; CLABSI = central line-associated bloodstream infection; VTE = venous thromboembolism.

developing PICC-related bloodstream infection include the underlying severity of the patients' illness, presence and stage of malignancy, and number of prior central venous catheter insertions.^{13,39,55} One way to operationalize these data may be for clinicians to avoid PICC placement in those who are critically ill, have aggressive malignancies associated with high rates of thrombosis, or have undergone multiple prior venous catheter insertions during the same hospitalization (eg, patients in the intensive care unit). Likewise, catheter-related risk factors for central line-associated bloodstream infection, such as route of placement (eg, greater risk associated with subclavian insertion), number of lumens, duration of implantation, nature of infusate, and the technique used to access and maintain the catheter, are pertinent when placing PICCs.^{8,35,37,44,55} Clinicians

should thus develop a strong rationale if placing PICCs for prolonged periods, PICCs with multiple lumens, or PICCs that may not always be cared for using aseptic precautions.

The Michigan Keystone Project has significantly advanced the science of bloodstream infection prevention in intensive care unit patients with central venous catheters.^{56,57} However, specific data regarding PICC-related infections were not collected and is not available for review (Pronovost P, personal correspondence, September 29, 2011). The latest bloodstream infection prevention guidelines exemplify this knowledge gap by only referencing to PICCs as the catheter of choice when intravenous therapy is anticipated to exceed 6 days. No specific recommendations regarding PICC-related bloodstream infection prevention strategies are made.⁵⁸ Furthermore, because many PICCs

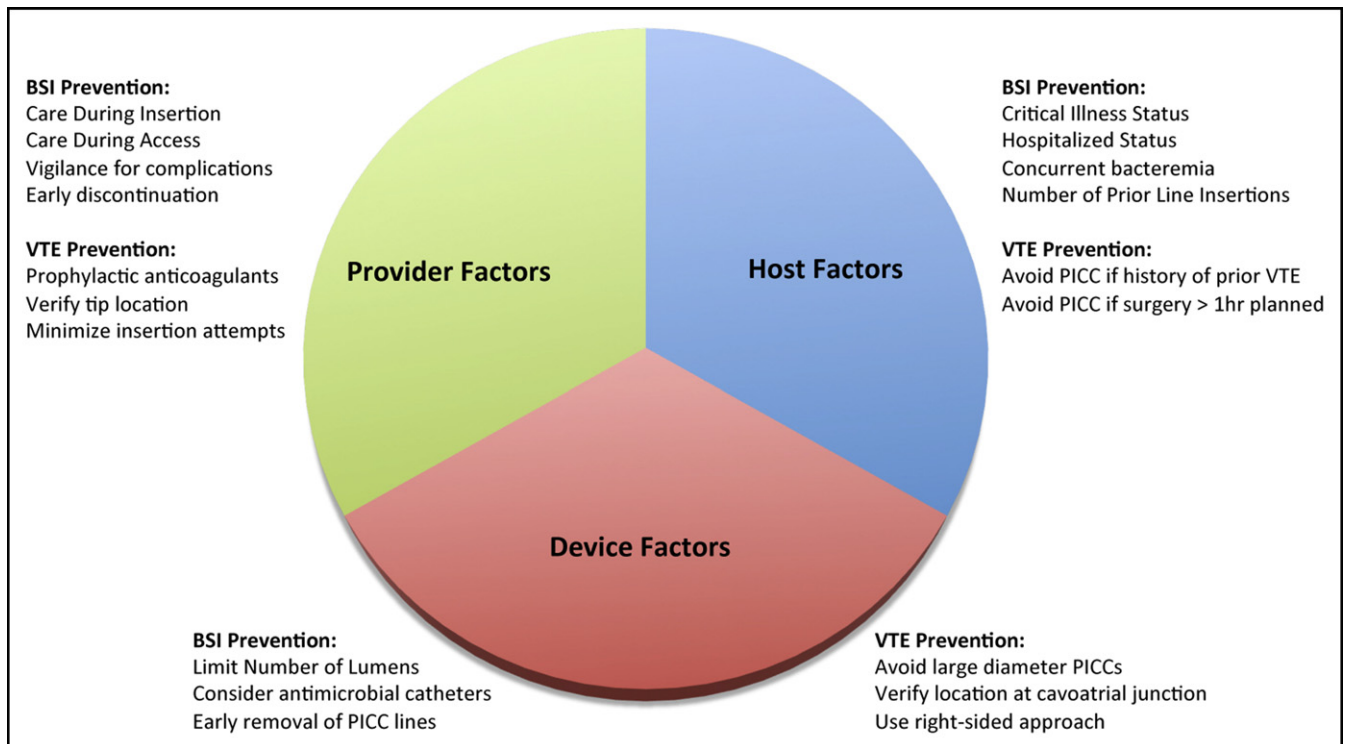


Figure Conceptual framework for prevention of PICC-related complications. BSI = bloodstream infection; PICC = peripherally inserted central catheter; VTE = venous thromboembolism.

are placed in non-intensive care unit settings and surveillance for bloodstream infections remains sparse in these areas, there is an extraordinary need for studies regarding the epidemiology and risk of central line-associated bloodstream infection in those with PICCs.^{59,60}

Prevention of Peripherally Inserted Central Catheter-Related Venous Thromboembolism. The optimal approach to prevent PICC-related thrombosis remains unclear. In both patients with and without malignancy, existing guidelines do not recommend the use of anticoagulants to reduce PICC-related venous thromboembolism absent medical conditions that may warrant such prophylaxis.^{61,62} However, a meta-analysis of 15 randomized controlled trials of anticoagulant prophylaxis in patients with central venous catheters concluded that the pooled relative risk was in favor of prophylaxis for preventing both symptomatic and asymptomatic deep vein thrombosis (relative risk, 0.31-0.73; $P < .001$).⁶³ Conversely, in patients with cancer with central venous catheters, a Cochrane systematic review concluded that the available evidence did not support the routine use of low-dose heparin or vitamin K antagonists.⁴⁷ These opposing conclusions are not surprising when one examines the variation in patient populations, PICC characteristics, dose/duration of venous thromboembolism prophylaxis, and method of venous thromboembolism detection (screening for asymptomatic vs symptomatic thrombosis) used in these studies. To date, no randomized controlled trial regarding the risks and benefits

of venous thromboembolism prophylaxis in ambulatory or hospitalized PICC recipients exists.

As with bloodstream infection prevention, the use of patient-, provider-, and catheter-dependent risk factors can help clinicians assess PICC-related venous thromboembolism risk. For instance, patients with a history of venous thromboembolism or those undergoing surgery lasting 1 hour or more are at high risk for PICC-related thrombosis.³³⁻³⁵ In the presence of these risk factors, abstaining from PICC placement or prescribing pharmacologic venous thromboembolism prophylaxis may be appropriate. PICC-specific parameters, such as larger-diameter PICCs or those placed for prolonged durations, also may trigger consideration of anticoagulant prophylaxis, because these characteristics are associated with thrombosis.^{34,38,47,64,65} Because certain medications (eg, mannitol, vancomycin) increase the risk of PICC-related venous thromboembolism, clinicians should not forget to consider the infusate when estimating PICC venous thromboembolism risk.^{35,37,42,66}

In a recent systematic review, verification and repositioning of the PICC tip at the cavoatrial junction was protective against thrombosis, a finding that may be physiologically explained by absence of venous stasis in this region.¹⁹ A subsequent study also found that patients whose PICC tip was located in regions other than the superior vena cava experienced greater venous thromboembolism (OR, 2.61; 95% CI, 1.28-5.35).³³ Thus, verification of PICC positioning represents an important aspect in the prevention of

PICC-related venous thromboembolism. Although some have theorized that repeated catheter manipulations to ensure positioning at this site may increase paradoxically the risk of infection, a study at the University of Michigan involving 1350 PICCs found no such relationship.⁶⁴

The Need for a Research Agenda Focusing on Peripherally Inserted Central Catheters

There is an unprecedented need for a research agenda that examines the benefits and risks related to PICC use. For example, a recent systematic review and meta-analysis found that PICCs were associated with greater overall complications than other central venous catheters (17% vs 10%; OR, 2.02; 95% CI, 1.26-3.24), including greater rates of thrombophlebitis (OR, 5.82; 95% CI, 2.37-14.20).¹⁹ Because no randomized controlled trials comparing the risk of venous thromboembolism or central line-associated bloodstream infection between PICCs and other central venous catheters exist, clinicians have no evidence to guide the decision regarding which central venous catheter is safest for their patients. This void represents a significant knowledge gap. Relatedly, current patterns and indications for PICC use remain largely unknown. Because many patients in non-intensive care unit settings receive PICCs, it is important to understand the rationale and risks associated with PICC use in this population, as placement in this subset may reflect inappropriate use. For instance, a recent study reported mean PICC dwell times of only 14.4 days in patients hospitalized in non-intensive care units; of note, PICC recipients in this study also had 5.4 concurrent days with a peripheral intravenous line, suggesting that venous access may not have been the rationale for PICC placement.⁹ Because each day with a venous catheter increases the risk of complications, indiscriminate use of PICCs has important cost and safety implications.^{67,68} Last, although our conceptual framework using patient-, provider-, and device-related characteristics seems logical, it is derived piecemeal from various studies and remains untested. Prospective studies of PICC recipients coupled with clinical outcomes are necessary to validate this model.

CONCLUSIONS

Although PICCs have become an indispensable tool in patient care, these seemingly ubiquitous devices are associated with important, often overlooked, complications. A research agenda dedicated to examining the appropriateness, safety, and comparative benefits from PICCs is needed to better guide the use of this technology.

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